METHOD FOR MAKING A BIODEGRADABLE ADHESIVE FOR SOFT LIVING TISSUE

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to medical adhesives and more particularly, to biodegradable adhesives for connecting soft tissue.

2. Description of the Prior Art

Typically, sutures are used to close incisions in soft tissue. There are, however, complications associated with the use of sutures. For example, tissue incompatibility with sutures often causes fistulas and granulomas. Even necroses can result if sutures restrict blood supply. Sutures also tend to cut through weak parenchymatous tissue and weak, poorly vascularized tissue. In microsurgery, the use of sutures requires special skills and time.

Researchers have, for some time, investigated the use of soft tissue adhesives. The major developments to date have primarily been cyanoacrylate adhesives, fibrin adhesives and gelatin/resorcinol/formaldehyde adhesives.

Cyanoacrylate adhesives were developed in 1959 and were first patented as tissue adhesives in 1973, U.S. Pat. No. 3,759,264. A variety of 2-cyanoacrylate esters can be synthesized by varying the length of the alkyl chain. Although the cyanoacrylates have demonstrated tremendous bonding strength, the degradation products, formaldehyde and alkyl cyanoacetate, cause tissue irritation. Methyl and ethyl cyanoacrylates biodegrade to produce high concentrations of toxic degradation products.

Fibrin adhesive systems are the only natural adhesive system now available. They are essentially two component systems comprised of concentrated human fibrinogen and thrombin and calcium chloride which coagulate when mixed. The fibrin adhesive systems are preferable to cyanoacrylate adhesives because they do not induce toxic or inflammatory responses. However, because the fibrinogen component is manufactured from pooled human blood, there is potential for possible immune reactions or transferral of infection, such as viral hepatitis "B" or human immunodeficiency virus.

Polyurethanes have also been investigated as tissue adhesives. Recent work with castor oil/isocyanate prepolymers of polyurethane indicates that the reactivity of these systems is somewhat slow. The reactivity was shown to increase by the synthesis and use of tetrafluoro 1,3-phenylene diisocyanate, but the adhesion is unsatisfactory compared to that of the cyanoacrylates. The polyurethane systems may also suffer from toxicity problems. These systems contain toxic monomeric diisocyanates, some of which can diffuse away from the reaction site before the reaction occurs. These systems also contain other noxious substances, such as pyridine and tetrahydrofuran. Such conventional polyurethanes are not biodegradable and are believed to act as a barrier to the regeneration of natural tissue.

Poly(methyl methacrylate) cement (PMMA) has been used in dentistry for some time and, more recently, in orthopaedic surgery. PMMA reportedly gives results that frequently do not hold up.

The proteinaceous gelatin/resorcinol/formaldehyde adhesive systems have been widely investigated. Studies to date have been favorable. This system is thought to cross-link with the tissue by condensation of phenolic residues with formaldehyde.

Lipatova et al. U.S. Pat. No. 4,057,535 describes an adhesive for gluing soft tissue comprised of aromatic diisocyanate (from 1 to 50 wt. %), 2, 4, 6-tris (dimethylaminomethyl) phenol (from 0.1 to 20 wt. %) and macrodiisocyanate of the general formula

$$NCO-R-NHCO-R'-NHCO-R-NCO,$$

where R is an aromatic diisocyanate radical and R' is a polyether or polyester radical (from 98.9 to 30 wt. %). The Lipatova adhesive biodegrades to ethylene glycol and a diester, neither of which have a normal metabolic function.

There are a number of polymers and copolymers of lactic acid and glycolic acid reported. The advantage of utilizing these copolymers is the fact that the hydrolysis products are constituents in normal metabolic pathways and, thus, are nontoxic. Schmitt et al. U.S. Pat. Nos. 3,463,158 and 3,867,190 describe applications for polyglycolic acid. Nevin U.S. Pat. No. 4,273,920 describes a process for making lactic-glycolic copolymers having molecular weights of about 6000 to about 35,000. Rosensaft et al. U.S. Pat. No. 4,243,775 describes a method for manufacturing surgical articles, such as sutures, from an absorbable copolymer of a glycolide monomer and a cyclic ester monomermade from lactide or selected from the group consisting of lactones, oxalates or carbonates. Tunc U.S. Pat. No. 4,539,981 describes an absorbable bone fixation device made from a high molecular weight polymer of L(-) lactide.

St. John U.S. Pat. No. 4,595,713 describes a medical putty for tissue augmentation comprising a copolymer of a major amount of epsilon caprolactone (60 to 95 wt. %) and a minor amount of lactide (40 to 5 wt. %). Depending upon the application, other components, such as osteogenic material or chopped carbon fiber, may also be included.

Based on research conducted to date, it is believed that no single adhesive is likely to be suited for all types of surgery. Several features of adhesives for soft biological tissue appear to be important. Primarily, the adhesive should be strong enough to hold the wound tissue together until natural tissue regeneration can occur. The adhesive material should be biodegradable and the degradation products should ideally be utilizable in the normal metabolic pathways of the recipient.

It is an object of the present invention to provide an adhesive, and a method for making such an adhesive, for use in augmenting sutures to hold soft biological tissue. It is a further object of the present invention to provide such an adhesive that is itself nontoxic and that yields nontoxic degradation products.

SUMMARY OF THE INVENTION

The present invention provides an adhesive and a method for making such an adhesive which is suited for use in joining soft living tissues, and is particularly well suited for augmenting sutures to join such tissue. The adhesive is comprised of a multifunctional resorbable polyester backbone having diisocyanate end groups wherein the polyester backbone is selected from the group consisting of polymers and copolymers of lactide, glycolide and ϵ-caprolactone. The polyester portion has